REMARKS

Status of the claims

Claims 1-3, 5-10, 12-15 and 19 are pending. Claims 1-3, 5-10, 12-15 and 19 are rejected. Claims 8, 13 and 19 are amended. Claims 1-7, 11, 16-18, and 20 are canceled.

Claim amendments

Claims 8, 13 and 19 are amended to recite that orally administered type one interferon is ingested by immediately swallowing it upon oral administration to overcome a rejection under 35 U.S.C. 103(a) over **Sobel** and **Cummins.** Support for these amendments is found in Applicant's specification as described in detail *infra*. Claim 13 is amended further to properly recite "human" and not "animal" in the body of the claim. Claims 1-7 are canceled. No new matter is added.

The 35 U.S.C. §102(e) rejection

Claims 1-3 and 6-7 stand rejected under 35 U.S.C. §102(e) as being anticipated by **Sobel** (U.S. Patent No. 5,780,021). Applicant respectfully traverses this rejection.

Applicants have canceled claims 1-3 and 6-7 thereby rendering the rejection moot. Accordingly, Applicants respectfully request that the rejection of claims 1-3 and 6-7 under 35 U.S.C. §102(e) be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 1-3, 5-10, 12-15 and 19 are rejected under 35 U.S.C. §103(a) as being obvious over **Sobel** and **Cummins** (U.S. Patent No. 5,019,382). Applicant respectfully traverses this rejection.

The Examiner maintains that **Sobel** teaches the oral administration (col. 13, ll. 10+) of a type I interferon for autoimmune diseases, including diabetes, but not particularly multiple sclerosis (col. 2, ll. 5-30), in the same doses claimed herein (col. 4, ll. 10-25). The species to be treated are taught (col. 4; col. 11, ll. 35+). Additionally, the Examiner states that **Sobel** teaches that the treatment reduces inflammatory response (col. 10), which would in turn reduce the levels of inflammatory cytokines and that it inhibits recurrent diabetes (col. 11, ll. 20). The Examiner also states that **Sobel** does not teach alternate day dosing nor multiple sclerosis in particular, although he does teach the therapy for auto-

immune diseases and it is well-known that multiple sclerosis is an autoimmune disease.

The Examiner states that **Cummins** also teaches all the limitations of the claims, including using alpha interferon for multiple sclerosis, except the amount claimed and alternate day dosing. The Examiner further states that **Cummins** does teach a single or multiple daily dose regimen and a staggered regimen of 1-3 days per week or month as an alternative to daily dosing (col. 5, ll. 50-55). The Examiner concludes that it would have been obvious to one of ordinary skill in the art to adopt an alternate day dosing and administer IFN as shown by **Cummins** for MS. The Examiner further points out that even though **Sobel** teaches the same amounts, the reference further states that the precise amount will depend on the judgement of the attending physician based on considerations of age, weight and condition of the patient. Applicant respectfully disagrees.

In U.S. Patent No. 5,780,021 **Sobel** states generally that administering an effective amount of a Type I interferon or a hybrid or analog or mixture thereof to a mammal prevents or treats autoimmune disorders (Abstract; col. 1, ll. 46-49). **Sobel** teaches that doses may range from 1×10^5 to 75×10^6 units, but may be 1 x

10^4 units or lower (col. 4, ll. 10-17). **Sobel** makes a general statement that the interferon may be administered orally, intravenously, intramuscularly, intraperitoneally, or subcutaneously (col. 4, ll. 24-28). **Sobel** generalizes that interferons may inhibit recurrent diabetes in transplanted pancreas or islet cells in a patient having Type I diabetes (col. 11, ll. 20-22). **Sobel** teaches that intraperitoneal delivery of 100,000 and 400,000 units of a hybrid interferon lowered the incidence of diabetes in DP-BB rats as demonstrated by survival curve analysis (col. 9, ll. 59 to col. 2, ll. 42).

Applicant submits that **Cummins** hypothesizes that contacting the oropharyngeal mucosa with interferon will potentiate disease-corrective immune responses in vertebrates with immuno-resistant disease states characterized by apparent hyper- or hypoactive immune system function, e.g., autoimmune disorders having chronic tissue degenerative inflammation such as multiple sclerosis. A dosage of about 0.1 to about 5 IU/lb is administered in a solution or in a novel solid unitary dosage form adapted to be dissolved in saliva when placed in the mouth (Abstract).

Applicants have canceled claims 1-3 and 5-7. As amended, Applicant's invention in claims 8, 13 and 19 is to

immediately swallowing an orally administered type one interferon to a human to ingest the same to reduce the frequency/severity of relapse in multiple sclerosis, to reduce inflammation associated with multiple sclerosis and to reduce cytokine levels associated with multiple sclerosis, respectively. The instant specification **clearly** and **specifically** teaches that human subjects having or not having multiple sclerosis ingested the interferon by taking the drug into the mouth and **immediately swallowing** (Applicants emphasis) with at least 150 mls of water, (pg. 11, ll. 9-10; pg. 14, ll. 6-8).

In humans serum ICAM-1 and IFN-γ were used as markers of inflammation. These are subclinical indicators of multiple sclerosis and the measured levels would indicate if a patient is experiencing a relapse and the severity thereof. Subjects with early relapsing-remitting multiple sclerosis demonstrated decreased levels of soluble serum ICAM-1 after swallowing different doses of interferon compared to levels prior to taking interferon (page 15, ll. 9-12; page 55, ll. 12-20; Figure 14).

Cummins does not teach immediately swallowing to ingest orally administered interferon, but rather that the interferon must remain in the oropharynx for sufficient time to contact and interact effectively with the oral mucosa for uptake and delivery to

a systemic location, as taught in **Cummins** (col. 4, ll. 13-18 & 37-41). **Cummins** teaches that it is critical that the interferon is administered in a dosage form adapted to dissolve in saliva to assure maximum contact with the oropharyngeal mucosa of the human or animal (col. 4, ll. 37-41). The dissolved interferon is held in the mouth about 15 secs to a minute, depending on the pharmaceutical carrier for the interferon to be absorbed and then spit out or swallowed (col. 12, ll. 25-29). Therefore, because spitting out the interferon is equivalent to swallowing the interferon, one of ordinary skill in the art may infer that no interferon or a negligible amount was remaining and that swallowing is merely an alternative means of eliminating the saliva and/or remaining solution from the mouth. Thus, benefit only is obtained from absorption of the interferon over time through the oropharyngeal mucosa.

In Applicant's invention, immediately swallowing the interferon causes it to effectively bypass the oropharyngeal mucosa. The interferon is not held in the mouth, in any form, long enough to contact and absorb into the oral mucosa. Additionally, swallowing with a quantity of water further precludes such contact. Regardless of whether or not ingestion of a drug encompasses absorption thereof through the oropharyngeal mucosa, a method utilizing this

step for absorbing interferon is significantly different from a method requiring that the interferon be immediately swallowed.

This is particularly so because the general knowledge in the art and in **Cummins** was that interferon, as a protein, would not survive the enzymes in the digestive process (col. 2, ll. 47+) and would not be transported across the gut mucosa (**Lecce** *et al.* J Mol Biotherapy 2:211, pg. 4 of 6 (1990), reference supplied previously). **Cummins** hypothesizes that the oral cavities of humans and animals contain receptors for interferon which, when bound, are involved in an immunomodulatory process resulting in a generalized elevation of immunocompetence in the host (**Lecce** *et al.* J Mol Biotherapy 2:211, pg. 5 of 6 (1990)), thus necessitating holding the interferon in the mouth for a period of time. Applicant has demonstrated in the instant invention that interferon can induce a response when delivered immediately to the stomach and small intestine and interacts with the gut mucosa, such as in a GALT-mediated response (pg. 64, ll. 18 to pg. 65, ll, 19). Therefore, **Cummins** effectively teaches away from the instant invention.

As such, the combination of **Sobel** and **Cummins** does not teach all the elements of the instant invention. Applicants strongly reiterate that **Cummins** does not teach immediately

swallowing the interferon. Additionally, Applicants submit that **Sobel** does not fairly teach oral administration of interferon. **Sobel** merely included a generic list of known routes of administration when, at best, parenteral administration is taught.

At a minimum, in considering what is suggested by the combination of **Sobel** and **Cummins**, one of ordinary skill in the art may be motivated to administer interferon using the doses of interferon taught in **Sobel**. However, and more importantly, the suggestion for one of ordinary skill in the art in combining **Sobel**'s generalization that interferon may be orally administered with **Cummins** method of oral administration would be to have the patient hold dissolved interferon within the oral cavity. The state of the art at the time of the instant invention and **Cummins** teach away from a reasonable expectation of success in treating an autoimmune disease if the interferon is swallowed.

Claims 2-3 and 5-7 depend from claim 1, claims 9-10 and 12 depend from amended claim 8 and claims 14-15 depend from amended claim 13. These dependent claims further limit the types of interferon and administration thereof to every other day. Applicants have canceled claims 1-3 and 5-7. Therefore, if the combination of **Sobel** and **Cummins** cannot render the instant

invention obvious as recited in amended claims 8 and 13, then neither can incorporating the limitations of the dependent claims render the invention obvious.

Obviousness requires a teaching of all the elements by the prior art with a motivation or suggestion to combine the prior art with a reasonable expectation of success. Thus, as discussed *supra*, lacking a teaching of swallowing orally administered interferon together with a teaching away from the use of swallowed interferon and the resultant lack of a reasonable expectation of success, the combination of **Sobel** and **Cummins** cannot render the instant invention obvious. Thus, the invention as a whole was not obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, in view of the claim amendments and arguments presented herein, Applicant respectfully requests that the rejection of claims 1-3, 5-10, 12-15 and 19 under 35 U.S.C. 103(a) be withdrawn.

This is intended to be a complete response to the Final Office Action mailed February 2, 2004. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. Applicant believes no fees are due, however, if this in error, please debit any

fees due from Deposit Account No. 07-1185 on which Applicant's counsel is allowed to draw.

Respectfully submitted,

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Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com